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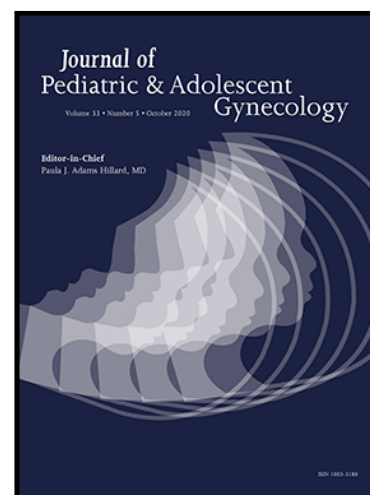
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Vulvar aphthous ulcer in an adolescent after Pfizer-BioNTech (BNT162b2) COVID-19 vaccination

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Abstract

Background: Vulvar aphthous ulcers are a rare type of genital lesion most common in non-sexually active adolescents. Vulvar aphthous ulcers are typically associated with viral infections. To date, there have been several cases reported in patients infected with COVID-19. Vulvar aphthous ulcers have not been previously reported in the literature following vaccination.

Case: We present the case of a 16-year-old adolescent who developed vulvar aphthous ulceration following Pfizer-BioNTech (BNT162b2) vaccination.

Summary and Conclusion: Through an extensive literature search, we found no previous reports of vulvar aphthous ulcer following vaccination. Our case highlights a potential novel side effect of Pfizer-BioNTech COVID-19 vaccination and a new etiology for vulvar aphthous ulcers. This case suggests that vulvar aphthous ulcers may be associated with COVID-19 vaccination through a yet undetermined mechanism that requires further investigation.

Key Words: Adolescent gynecology, pediatric gynecology, vulvar aphthous ulcer, COVID-19, vaccine

Introduction

Aphthous ulcers, otherwise known as Lipschütz ulcers, acute genital ulcers, and acquired genital ulceration, represent a painful, distressing condition of the vulva and lower vagina that overwhelming

affects non-sexually active adolescent females. While the majority of genital ulcers are sexually transmitted, aphthous ulcers are the most common cause of non-transmissible vulvar ulcers. Patients typically present with sudden onset of one or multiple genital ulcerative lesions coupled with an influenza-like prodrome. Lesions are typically large, red and erosive, ranging from 0.3 – 5 cm in one study.¹ A violaceous border, necrotic base and fibrinous exudate are other key features of the lesions.²

The underlying pathogenesis of vulvar aphthous ulcers is unclear. Numerous case reports have described aphthous ulcers as a dysregulated immune response associated with a variety of infections including cytomegalovirus (CMV), influenza, mumps virus, salmonella, mycoplasma and most notably, Epstein Barr virus (EBV).¹ In a case series of 13 pubertal females, 31% of vulvar aphthous ulcers were associated with EBV.² Vulvar aphthous ulcers have also presented as a cutaneous manifestation of noninfectious conditions such as Behcet's disease and Crohn's disease.²

Over 334,000,000 doses of the Moderna, Pfizer and Johnson & Johnson vaccine have been administered since December of 2020. Side effects are common and have been widely reported. In a prospective observational study conducted using data from the COVID Symptom study application, 22% of 28,207 patients reported systemic side effects after receiving the second dose of Pfizer BioNTech (BNT162b2) vaccine.³ Headache, fatigue, chills, diarrhea, fever and myalgias were common systemic side effects, while local side effects included pain, swelling, tenderness and itching.

Skin manifestations have been observed following the Moderna (mRNA-1273) and Pfizer-BioNTech (BNT162b2) vaccines. In one study, delayed injection-site reaction was present in 2.1% of subjects with 4.9% demonstrating disseminated lesions. Histologic examination revealed neutrophils, dilated vessels and lymphocytic infiltration.⁴ These manifestations were hypothesized to be a hypersensitivity reaction either to the spike protein or some other component of the vaccine.

In this report, we present the case of a patient presenting with vulvar aphthous ulcer following Pfizer BioNTech (BNT162b2) COVID-19 vaccination. Furthermore, this is the first case report to describe

vulvar aphthous ulcer after vaccination, among both mRNA and conventional vaccines. The objectives of this case report are to highlight a novel etiology of vulvar aphthous ulcer and discuss potential mechanisms of disease.

Case

A 16-year-old non-sexually active female presented to the pediatric gynecology clinic with vaginal pain. Six days prior she had received her second dose of the Pfizer BioNTech (BNT162b2) COVID-19 vaccine. Within 24 hours of receiving the vaccine, she developed fever, fatigue, myalgias and “sores” in her vaginal area. Over the next 2 days, right sided lesions in her vaginal area coalesced and became more painful. She presented to urgent care with a fever of 105 degrees Fahrenheit where she was diagnosed with a Bartholin gland abscess and prescribed amoxicillin-clavulanate. Despite antibiotic therapy, her symptoms continued to worsen prompting her to return to clinic two days later. By this point, the lesions were covered in exudate with a necrotic, ring-like border. Gynecology was consulted and recommended assessment for likely Lipschütz ulcers.

In gynecology clinic, the patient’s lesions were exquisitely painful, resulting in difficulty with urination, defecation, and walking. She had no respiratory symptoms and no known COVID-19 exposures. Her medical history was significant for several congenital conditions requiring corrective surgeries including soft palate cleft, club foot, syndactyly of her left foot and congenital hearing impairment in the right ear. Additionally, the patient reported a history of recurrent oral ulcerations, but no previous history of genital ulcerations. Her family history was notable for “severe canker sores” in her father and uncle requiring medical intervention and hospitalization. The patient denied any history of sexual activity.

On exam, the patient was afebrile and in no acute distress. Her genitourinary exam was significant for an ulcerated lesion with adherent yellow and grey fibrinous exudate on the right labia minora measuring 3 cm x 2 cm (Figure 1A, B). The ulcer was well-demarcated with a necrotic appearing border.

Desquamation was observed of the surrounding tissue and the posterior fourchette. The affected right labia was markedly swollen in comparison to the left.

Laboratory evaluation was negative for SARS-COV-2 RNA by anterior nares swab. Viral polymerase chain reaction testing of the vulvar lesion was negative for herpes simplex virus (HSV) 1 and 2 as well as serum testing for HSV 1 and 2 antibodies. Epstein Barr nuclear antigen (EBNA) antibodies were present, indicating prior infection with EBV. Testing for CMV, syphilis (RPR), and human immunodeficiency virus (HIV) were negative. Fluorescent antinuclear antibody screen was negative.

Clinical history and genital examination findings were consistent with vulvar aphthous ulcers in association with influenza-like symptoms following Pfizer BioNTech (BNT162b2) COVID-19 vaccination. The patient was prescribed topical clobetasol 0.05% ointment and instructed to apply to the affected area twice daily for 14 days. Her pain management regimen included ibuprofen and acetaminophen as needed, as well as topical lidocaine gel. She was started on norethindrone 5 mg orally daily for menstrual suppression while her ulcerations were healing.

She presented for follow up two weeks later and reported improvement in her symptoms, although she was experiencing sensitivity with vulvar manipulation and pain with urination. The ulcerated lesion was noted to be resolving along the medial aspect of the right vaginal introitus (Figure 2). Vulvar edema had resolved. She reported the appearance of an oral ulcer several days prior and physical exam was consistent with aphthous ulcer on the inner aspect of her lower lip. Patient was referred to rheumatology in light of her recurrent oral aphthous ulcers, vulvar ulcer and family history of oral ulcerations. The case was submitted to the Centers for Disease Control and Prevention's (CDC) Vaccine Adverse Event Reporting System (VAERS) due to the temporal relationship with COVID vaccine administration.

Summary and Conclusions

This is the first case report to describe a potential relationship between the development of vulvar aphthous ulcers and COVID-19 vaccination. Our patient had typical clinical features of aphthous ulcer

including an influenza-like prodrome and characteristic dermatologic manifestations which occurred after receiving the Pfizer COVID vaccine.

Vulvar aphthous ulcers are thought to be precipitated by physiologic stress from a variety of insults, most notably viral infections. EBV is the common virus associated with vulvar aphthous ulcers. However, in many patients there is no evidence of recent infection, leading many to hypothesize that EBV infection alone cannot explain the majority of vulvar aphthous ulcer cases. Of note, there are two case reports of vulvar aphthous ulcer occurring in an adolescent and 41-year-old woman secondary to COVID-19 infection.^{6,7}

To our knowledge, aphthous ulcers have not been described in the literature following vaccination, both against COVID-19 and other non-COVID-19 pathogens. Since 1980, approximately 80% of the 164 cases of genital ulceration reported to the VAERS have been associated with COVID-19 vaccination. For the remaining 14 vaccines¹, 31 cases have been reported.⁵ A review of the VAERS, reveals 368 cases of oral aphthous ulcer and 126 cases of either genital, vaginal, vulval or vulvovaginal ulceration associated with COVID-19 vaccination.⁵ Of those involving the genitalia, 83 cases were associated with the Pfizer BioNTech (BNT162b2) vaccine.

COVID-19 vaccination has been associated with a myriad of systemic and local side effects, some of which mimic natural infection. The Pfizer BioNTech (BNT162b2) COVID-19 vaccine, which our patient received, is a lipid nanoparticle-formulated nucleoside-modified mRNA that encodes the receptor binding domain of the SARS-CoV-2 spike glycoprotein.⁸ The spike glycoprotein is a popular target in COVID-19 vaccine development as it mediates the entry of SARS-CoV-2 into host cells through binding the angiotensin-converting enzyme 2 receptor.

¹ Anthrax Vaccine, Hepatitis A, Human Papillomavirus Recombinant Vaccine (HPV4), Human Papillomavirus Recombinant Vaccine (HPV9), Influenza Virus Vaccine Quadrivalent, Influenza Virus Vaccine Trivalent, Meningococcal Vaccine, Pneumococcal Vaccine, Smallpox Vaccine, Tetanus and Diphtheria Toxoids, Typhoid vaccine, Varivax-Varicella Virus Live, Yellow Fever Vaccine, Zoster Vaccine.

Preliminary studies indicate that vaccination with Pfizer BioNTech (BNT162b2) elicits a strong host response, including activation of CD4+ and CD8+ T cells and release of immune-modulatory cytokines such as interferon gamma.⁸ In several studies, oral aphthous ulcers demonstrate local and systemic predominance of Th1 cytokine production including interferon-gamma.⁹ Oral aphthous ulcers are thought to have a similar underlying etiology to vulvar aphthous ulcers given the high rate of association between oral and vulvar aphthous ulcers in individual patients.¹ The temporal relationship of our patient's symptoms to Pfizer BioNTech (BNT162b2) vaccination in the context of a negative test for SARS-COV-2 RNA, as well as other infectious etiologies, suggest that her systemic symptoms and vulvar aphthous ulcer may have occurred secondary to an immune response precipitated by the vaccine. However, there are several other factors in this patient, including evidence of past infection with EBV and medical and family history of recurrent oral ulcers, which potentially contributed to their presentation.

In summary, this case highlights a potential novel association between mRNA Pfizer BioNTech (BNT162b2) COVID-19 vaccination and vulvar aphthous ulcer. Vulvar aphthous ulcers have been described in association with systemic viral illnesses including EBV, CMV and COVID-19. Our goal is to add to the literature a report of a seemingly rare, but not insignificant complication of the Pfizer BioNTech (BNT162b2) COVID-19 vaccine. This case suggests that vulvar aphthous ulcers may be precipitated by vaccination, however, further research is required to establish a causal relationship. One proposed mechanism for study is to investigate how the immune system's response to vaccination recapitulates the pro-inflammatory response associated with vulvar aphthous ulcers secondary to viral illness.

Declaration of Competing Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Figure 1. Initial presentation of the patient's vulva demonstrating edema (A) and an ulcerated lesion involving the right labia (B) with adherent yellow/grey fibrinous exudate and a necrotic appearing border. Patient providing labial traction.



Figure 2. Follow-up image 11 days later demonstrating a resolving ulcerated lesion along the medial aspect of the right vaginal introitus with scattered areas of overlying fibrinous material. Patient providing labial traction.